PROTOCOL TITLE:

Using Ultrasound Elastography to Predict Development of Sinusoidal Obstruction Syndrome

NCT03858530

PRINCIPAL INVESTIGATOR:

Sherwin Chan, MD PhD
Department of Radiology
816-324-3273
sschan@cmh.edu

Co-Investigator:
Rakesh Goyal, MD
Department of Hematology/Oncology
Rgoyal@cmh.edu

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REVISION HISTORY

This Revision History table is provided for the benefit of study team version control. If this table will not be useful to your team, you do not need to include it.

Revision #	Version Date	Summary of Changes	Consent Change?
2	1-28-2019	Adding CEUS exams	Y
3	2-28-2019	Revising CEUS language	Y
4	5-16-2019	Adding patient calendar handouts	N
5	6-5-2019	Blinding clinicians from results	Y
6	1-31-2020	Adding CIBTR data collection	Y

7	4-7-2020	Adding Dr. Averkiou and University of Washington to study	N

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1.0 Study Summary

Study Title	Using Ultrasound Elastography to Predict Development of Sinusoidal Obstruction Syndrome
Study Design	Single-site prospective cohort study to evaluate grayscale US, Doppler US, CEUS and SWE examinations in BMT patients younger than 21 years.
Primary Objective	Our central hypothesis is that SWE changes will precede clinical and conventional ultrasound diagnostic criteria for SOS. We would like to perform a prospective cohort trial to establish optimal timing to test for SOS using SWE.
Secondary Objective(s)	a) Determine if SWE can provide earlier SOS diagnosis compared to clinical criteria and b) Quantify the difference in SWE values between SOS patients who would benefit from drug treatment versus those who do well with supportive care c) Quantify relative ability of CEUS parameters versus grayscale and Doppler ultrasound.
Research Intervention(s)/ Investigational Agent(s)	Shear wave ultrasound elastography (SWE) Lumason (sulfur hexafluoride lipid-type A microspheres) injectable suspension
IND/IDE #	
Study Population	Children and adults, ages 1 month through 21 years who are undergoing allogenic or autologous myeloablative stem cell transplant.
Sample Size	80 patients
Study Duration for Individual Participants	Until discharge from BMT admission or to Day +100 after BMT, whichever comes first.
Study Specific Abbreviations/ Definitions	BMT: Blood and Marrow Transplant CEUS: Contrast Enhanced Ultrasound SOS: Sinusoidal Obstruction Syndrome SWE: Shear Wave Elastography US: Ultrasound VOD: Veno Occlusive Disease

2.0 Objectives

2.1 Our central hypothesis is that SWE changes will precede clinical and conventional ultrasound diagnostic criteria for SOS. We would like to perform a prospective cohort trial to establish optimal timing to test for SOS using SWE

2.2 Determine if SWE can provide earlier SOS diagnosis compared to clinical criteria.

2.3 Quantify the difference in SWE values between SOS patients who would benefit from drug treatment versus those who do well with supportive care.

2.4 Quantify relative ability of CEUS parameters versus grayscale and Doppler ultrasound

3.0 Background

3.1 Hepatic sinusoidal obstructive syndrome (SOS) is a complication of blood and marrow transplant (BMT) that is associated with high morbidity and mortality. 57,000 patients in the United States and Europe undergo BMT annually (1, 2), and SOS affects up to 15% of these patients (3). SOS pathogenesis is thought to be caused by damage to the hepatic venous endothelium due to the preparative regimen used before BMT. This damage results in obstruction of blood flow through the liver. Pathology shows collagen deposition in the sinusoids and fibrosis of venous lumens (10). The severity of the disease is correlated to the number and severity of the histological changes. Mild and moderate SOS can resolve with supportive treatment. Severe SOS (30% of SOS) is commonly associated with multi-organ failure and has a mortality rate of 80% despite available prophylaxis and treatment (Table 1) (4).

Table 1. Staging of VOD/SOS [20]

Mild : Resolved without interventions
Moderate : Requires treatment • Bilirubin > 6 mg/dl • AST > 5 times upper limit of normal • Weight gain > 5 % • Ascites
Severe : Progression to Multi-organ dysfunction syndrome • Respiratory failure (O2 saturation < 90 %) • Hepato renal syndrome • Encephalopathy

- Severe renal failure (creatinine > x 2)
- Bilirubin > 20 mg/ dl

SOS is most commonly defined by two clinical criteria: the modified Seattle criteria and the Baltimore criteria (Table 2) (11, 12). The modified Seattle criteria state that at least two of the following criteria must be present within 20 days of BMT: bilirubin ≥ 2mg/dL; hepatomegaly and/or ascites; and/or weight gain ≥ 5% above baseline weight (11). Pediatric SOS incidence in BMT is 20% and is higher compared to adults (13-15). Death or multi-organ dysfunction affects 30-60% children who develop SOS (16, 17). The most common definition of severe SOS is retrospective, namely death from SOS-related causes or persistent multi-organ dysfunction at 100 days post BMT. However, the European Society for Blood and Marrow Transplantation has proposed a new prospective SOS grading scheme that will likely become standard of care since it is pediatric patient specific and it is can be performed prospectively and thus can guide treatment (5).

Table 2. A table to show the clinical criteria for veno-occlusive disease

Modified Seattle Criteria Two of the following criteria must be present with in 20 days of SCT	***Baltimore Criteria*** Bilirubin must be ≥ 2mg/dL before 21 days SCT and two of the following criteria must be present
Bilirubin ≥ 2mg/dL	Ascites (Physical exam or radiographic)
Hepatomegaly increased over baseline	Weight gain ≥ 5 %above baseline weight *
Ascites (Physical exam or radiographic) and /or Weight gain ≥ 5 %above baseline weight	Hepatomegaly increased over baseline

3.2 Recently, a promising drug for SOS treatment has been discovered, defibrotide, which is a DNA derivative from porcine intestine that protects and repairs endothelial cells. Prior trials showed that defibrotide decreased the incidence of multi-organ failure and death from SOS. The main caveat is that treatment must be initiated very close to the time of clinical diagnosis using the Baltimore criteria to be effective (7). A study showed that 31/33 (94%) patients had complete remission of their SOS when treated with defibrotide <3 days after diagnosis, whereas only 3/12 (25%) patients had complete remission when treated >3 days of diagnosis (7). However, universal

prophylaxis is infeasible due to high drug costs ($155,000 for patient) (8). There is a critical need for an early and effective SOS diagnostic test that can identify patients who would benefit from defibrotide treatment.

Several adult and pediatric prospective studies have evaluated the efficacy of grayscale and Doppler ultrasound (US) in diagnosing SOS (18-20) and have concluded that the clinical criteria are superior to US criteria for SOS diagnosis. The main reason for this conclusion is that conventional US is able to diagnose SOS only after the clinical diagnosis (18-20). This research has resulted in multiple recent guidelines recommending US only for confirming clinical diagnoses or following disease progression and not for primary diagnosis (5, 6). Ultrasound shear wave elastography (SWE) has been shown to effectively diagnose passive hepatic congestion. Fontan physiology is the best studied example. SWE values markedly increased after the Fontan operation. This surgery connects the hepatic venous circulation to the pulmonary arteries exposing the liver to increased resistance from the pulmonary circulation thereby increasing hepatic venous congestion (21). Additionally, the effect sizes in the Fontan studies are large compared with the effect sizes in hepatic fibrosis studies (21, 22). The common thread of hepatic venous congestion between Fontan physiology and SOS physiology led us to hypothesize that SWE could be useful in SOS diagnosis. Additionally, preliminary SWE studies in adults showed that it might be useful in the setting of SOS (23). In addition to SWE, the use of contrast-enhanced ultrasound (CEUS) for evaluation of variability of blood flow in patients with SOS versus those without has also become of interest.

CEUS uses an intravenous injection of microbubble contrast agents and is an established method to detect and characterize focal liver lesions; it also has been used to diagnose liver vein thrombosis. [Wilson, Abdom Radiol (NY), 2018; Dietrich, Ultrasound Int Open, 2018; Trenker, BMT, 2018] The value of CEUS in VOD/SOS is evolving; however, the findings from two case reports suggest that the performance of CEUS could help to facilitate an early diagnosis and clinical follow-up of VOD/SOS. [Fontanilla, J Ultrasound Med, 2011; Trenker, BMT, 2018] For example, in a case report of a patient who developed signs and symptoms of VOD/SOS 44 days after HSCT, CEUS showed heterogeneous uptake of contrast in VOD/SOS, and the areas of delayed enhancement corresponded to stiff areas on SWE; the contrast-enhanced sonographic pattern normalized after specific treatment. [Fontanilla, J Ultrasound Med, 2011] In another case report—this one in a patient with a clinical diagnosis of VOD/SOS after HSCT—CEUS showed a normal arterial and portal venous contrast medium inflow, but almost no portal venous and parenchymal hepatic enhancement. [Trenker,

BMT, 2018] The CEUS findings were novel, representing VOD/SOS pathophysiology and hepatic microvascularization dysfunction for the first time. [Trenker, BMT, 2018] Since SOS is a heterogeneous disease, we believe that contrast enhanced ultrasound may be useful in characterizing areas that are more severely involved in SOS and areas that are less severely involved. By interrogating both areas using contrast kinetics and SWE and correlating the values to disease severity, we hope to gain more insight into which areas (severely involved or less severely involved) are most responsible for the clinical sequelae and outcomes in SOS.

3.3 The long-term goal of our research is to accurately identify SOS patients who would benefit from defibrotide treatment using US SWE. The overall objective of this study is to validate SWE as an early diagnostic marker for SOS. Our central hypothesis is that SWE changes will precede clinical and conventional US diagnostic criteria for SOS. Our hypothesis has been formulated on the basis of our own preliminary data. We completed the first prospective cohort trial demonstrating that US SWE provides SOS diagnosis (80% sensitivity and 67% specificity) nine days earlier than current clinical criteria (9). SWE is widely available, has no known side effects, and is easy to learn and interpret. Our study enrolled 25 high-risk BMT patients over 18 months (five with SOS and two with severe SOS). More data is needed to determine the optimal window for testing to balance between improved test characteristics and early detection of disease. We propose conducting a prospective cohort study with 80 additional patients, 12 of which will likely develop SOS (including four with severe SOS) to optimize SWE timing. This study will increase the confidence in the findings from our preliminary study and allow us to test SWE against newly published clinical criteria. The rationale for the proposed research is that, if SWE can diagnose SOS earlier than clinical criteria, then SWE can guide early initiation of SOS treatment.

4.0 Study Endpoints

4.1 To perform a prospective cohort trial to establish optimal timing to test for SOS using SWE.

4.2 Determine if SWE can provide earlier SOS diagnosis compared to clinical criteria.

4.3 Quantify the difference in SWE values between SOS patient who would benefit from drug treatment versus those who do well with supportive care.

4.4 Quantify relative ability to CEUS parameters versus grayscale and Doppler ultrasound.

5.0 Study Intervention/Investigational Agent

5.1 Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is used to prepare the ultrasound contrast agent. The single use kit contains the following three items:

- One clear glass 10mL vial containing 25mg of lyophilized powder lipid-type A, 60.7 mg of sulfur hexafluoride gas and capped with a blue flip-cap
- One prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent)
- One Mini-Spike

Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg of polyethylene glycol 4000, 0.19 mg of distearoylphosphatidyl-choline (DSPC), 0.19 mg of dipalmitoylphosphatidylglycerol sodium (DPPG-Na) and 0.04 mg of palmitic acid. The headspace of each vial contains 6.07 mg/mL (± 2 %) sulfur hexafluoride, SF6, or 60.7 mg per vial.

Each prefilled syringe with 5 mL of diluent 0.9% Sodium Chloride Injection is sterile, nonpyrogenic, preservative free containing 9 mg sodium chloride per mL.

Upon reconstitution with 5mL diluent, Lumason is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5; it is only for intravenous administration.

The sulfur hexafluoride lipid microspheres are composed of SF6 gas in the core surrounded by an outer shell monolayer of phospholipids consisting DSPC and DPPG-Na with palmitic acid as a stabilizer. Sulfur hexafluoride has a molecular weight of 145.9. Each milliliter of reconstituted Lumason suspension contains 1.5 to 5.6 x108 microspheres, 68 mcg SF6 (12 mcL), 0.038 mg DSPC, 0.038 mg DPPG-Na, 4.91 mg polyethylene glycol 4000 and 0.008 mg palmitic acid. The sulfur hexafluoride associated with the microspheres suspension is 45 mcg/mL. Fifteen to twenty three percent of the total lipids in the suspension are associated with the microspheres. The sulfur hexafluoride lipid microsphere characteristics are listed in Table 2:

Microsphere Characteristics	
Mean diameter range	1.5 – 2.5 μm
Percent of microspheres	≤ 10 μm ≥ 99%
Upper size limit	100.0% ≤ 20 μm

6.0 Procedures Involved

6.1 Single-site prospective cohort study to evaluate grayscale US, Doppler US, CEUS and SWE examinations in BMT patients younger than 21 years. Patients will be identified by the study team during a weekly conference that involves the study team and the Children's Mercy BMT team. All eligible patients will be approached for written informed consent by a member of the study team and if they consent, then they will be enrolled into the study prior to the start of their conditioning regimen.

Ultrasound Examinations and Timeline

After enrollment and within two weeks prior to starting their conditioning regimen, a limited abdominal US with Doppler measurements of the hepatic arteries, hepatic and portal veins, contrast enhanced ultrasound (CEUS) of the liver, as well as SWE will be performed.

Subjects will be undergo US examinations based on disease course as outlined below:

1. All Patients: Patients will undergo limited abdominal US with Doppler, CEUS and SWE once a week upon admission for conditioning until the patient day +30 BMT or discharge, whichever comes first.

2. Inpatient SOS: patients will undergo limited abdominal US with Doppler, CEUS and SWE once a week upon admission for conditioning until resolution of SOS.

3. Late Onset SOS: patients will undergo limited abdominal US with Doppler, CEUS and SWE once a week upon admission for conditioning until resolution of SOS.

The clinical team will order US, CEUS and SWE exams when patients have clinical suspicion for SOS and we will include these exams in our analysis. All imaging will be performed using GE Logiq E9 US machines by dedicated pediatric sonographers and interpreted by board-certified pediatric radiologists. Twelve shear wave velocity measurements will be taken 2-3 cm below the liver capsule at the mid-clavicular line in the right hepatic lobe and another 12 will be taken in the left hepatic lobe near midline

avoiding areas of vasculature (24). By necessity, the sonographer and interpreting radiologist will not be blinded to the clinical status of the patient. US and clinical data will be collected weekly and managed using REDCap electronic data capture tools hosted at Children's Mercy Hospital (25).

Table 3. Ultrasound Timeline

	ALL PATIENTS		INPATIENT SOS	LATE ONSET SOS
	Prior to Conditioning	**Start of Conditioning through Day +30**	**Through Resolution of SOS**	**Through Resolution of SOS**
	Screening	**Once per Week**	**Once per Week**	**Once per Week**
Limited Abdomen and Limited Abdominal Doppler Ultrasound	**X**	**X**	**X**	**X**
Contrast Enhanced Ultrasound	**X**	**X**	**X**	**X**
Ultrasound Elastography	**X**	**X**	**X**	**X**

6.2 Describe:

- There are no known risks to medical ultrasound imaging.
- CEUS Lumason® (sulfur hexafluoride lipid type-A microspheres) will be obtained through IDS pharmacy and administered through an already existing IV catheter by an RN or a radiology technologist trained and certified to administer the Lumason® contrast agent, and an abdominal ultrasound will be completed.
- Lumason (sulfur hexafluoride lipid-type A microspheres) is the investigational product. The recommended dose of Lumason for children is 0.03 mL/kg up to a maximum dose of 2.4mL injected into a peripheral intravenous catheter. See individualization of dose below.

  1. Follow the Lumason injection with a flush of 5 ml of 0.9% Sodium Chloride Injection, USP.
  2. The maximum total dose for children as listed in the package insert should not exceed 2.4 mL in any 10-minute period. With a maximal total dose of 4.8 mL in any one patient during a single exam.

6.3 Protected health information (PHI) to be collected for the purpose of this study alone will include; MRN, date of transplant, dates of ultrasound exams (attached data collection sheet). This information will be documented in RedCap. Within RedCap, there will be two separate files. One file will include minimal PHI (dates of service) and contain study data according to an assigned study ID number. The second file, will contain a master list of subjects linking the subject PHI with the assigned study ID number. The research record generated will consist of an excel spreadsheet from the data dictionary within RedCap. Security measures include: storage of the data on a password protected computer in a restricted assess departmental folder limited to only study personnel.

6.4 Participants in this study have two options regarding data collection, they may consent to take part in the CIBMTR Research Database or they may take part in only this study.

Data Collection Procedures for those that consent to take part in the CIBMTR Research Database:

Subjects may have already consented to take part in the CIBMTR Research Database (IRB# 11120281). If they are not yet taking part in that study, they will be given the option to consent for CIBMTR Research Database at the time they are consenting for this study.

If a subject chooses to take part in the CIBMTR database, data entered as part of this protocol will be entered into the CIBMTR database at the end of local site enrollment.

Data will provided to CIBMTR in the form of a spreadsheet and will be password protected and sent to CMH only for data analysis.

Clinical and outcome data, including DOB, dates of service, exams, lab values and clinical timepoints will be evaluated.

Data Collection Procedures for those that <u>do not</u> consent to take part in the CIBMTR Research Database:

For subjects that consent to BMT Elastography (Internal) study, but do not consent to have their data entered into the CIBMTR database will have their clinical variables entered into a local REDCap database. Those data points will include DOB, dates of service, exams, lab values and clinical timepoints

Data Collection Procedures for both groups:

Additional clinical variables (not captured in the CIBMTR database needed to define our objectives) and elastography variables will be retrospectively extracted from the patients' electronic medical records and entered into REDCap. We will collect a number of variables based on the CIBMTR +100 Day outcome form and we will collect variables related to the modified Seattle criteria,

Baltimore criteria and the new EBMT criteria. We will also collect clinical and laboratory parameters of liver disease to help us evaluate for other hepatic complications from HCT. We will use the adult and pediatric EBMT criteria to determine the date on which the patient was first diagnosed with SOS. The date of diagnosis will be the first day on which the patient meets the EBMT criteria for their cohort (adult or pediatric). We will also use clinical data to grade SOS severity, to detect other hepatic complications from HCT, and to inform our SOS predictive modeling. For SOS grading, the day on which the patient meets the severity criteria for that particular grade will be recorded.

7.0 Data and Specimen Banking

7.1 N/A

8.0 Genetic Analysis Information

8.1 N/A

9.0 Sharing of Results with Subjects

9.1 US SWE results will be blinded from clinicians and patients.

9.2 Any unexpected findings will be communicated to the ordering physician by Dr. Chan via phone or email.

10.0 Study Timelines

10.1 Describe:

- An individual's participation in the study will be during their inpatient stay for their BMT. Once the patient is discharged or Day +100 after BMT is reached, whichever comes first, subject will no longer be in the study.
- July 1, 2018 through June 30, 2020
- June 30, 2021

11.0 Inclusion and Exclusion Criteria

11.1 Describe the criteria that define who will be included or excluded in your final study sample.

Inclusion Criteria

- Subject's age 1 month through 21 years whom are undergoing myeloblative conditioning regimen prior to BMT are eligible for the study.
- Subjects will be identified by treating BMT physician
- 1 month through 21 years

- July 1, 2018 through June 30, 2020

Exclusion Criteria

- Any other medical or social condition that in the opinion of the investigator would make them unsuitable to participate.

- Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the following populations as subjects in your research unless you indicate this in your inclusion criteria.)

  - Adults unable to consent: Include
  - Individuals who are not yet adults: Include
  - Pregnant women: Exclude
  - Prisoners: Exclude
  - Wards of the state: Exclude

12.0 Vulnerable Populations

12.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- All subjects and family will be given sufficient time to review and determine if they would like to participate in the study.
- Subjects over the age of 7 will be required to provide assent for study procedures. Subject enrollment is completely voluntary.

13.0 Local Number of Subjects

13.1 We anticipate enrolling 80 subjects.

14.0 Screening and Recruitment Methods

14.1 Candidates for the study will be identified by BMT physician and approached for consent prior to start of conditioning regimen.

14.2 BMT patients are the source of subjects

14.3 Subjects will be identified and referred by BMT provider

14.4 A Waiver of HIPAA Authorization for Recruitment purposes only is requested to ensure subjects meet eligibility criteria for enrollment. Pre-screening information will not be recorded.

14.5 Subjects will be informed of the study by their treating BMT physician and then approached by a member of the study team for consent.

15.0 Reimbursement, Payment and Tangible Property provided to subjects

15.1 N/A

16.0 Withdrawal of Subjects

16.1 Subjects may be withdrawn at the discretion of their treating physician or at the LAR/subject request at any time during their inpatient stay. All data collected prior to the date of withdrawal will be kept for analysis.

16.2 Notification of request of withdrawal to study team is required

16.3 This is a minimal risk study, thus no follow-up is needed.

17.0 Risks to Subjects

17.1 We do not anticipate any additional risks to this study as all patients will already have IV access per SOC for BMT and no additional line placements will be required as part of this study. All subjects will be monitored during the Lumason CEUS examination by radiology personnel and by BMT staff after the exam for any adverse events.

Reported risks related to Lumason administration include:

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly in adults during or shortly following administration of ultrasound contrast agents, including Lumason. These reactions typically occurred within 30 minutes of administration. Hypersensitivity reactions such as skin erythema, rash, urticaria, flushing, throat tightness, dyspnea, or anaphylactic shock have uncommonly been observed following the injection of Lumason. The exclusion criteria eliminate any subjects with a known cardiac abnormality or a known sensitivity to sulfur hexafluoride, so we do not anticipate that these reactions will occur. Resuscitation personnel and equipment will be available during the study treatment and follow-up period.

Adverse Reaction	Number	(%)
Any Adverse Reaction	340	5
Headache	65	1
Nausea	37	0.5
Dysgeusia	29	0.4
Injection site pain	23	0.3
Feeling hot	18	0.3
Chest discomfort	17	0.2
Chest pain	12	0.2
Dizziness	11	0.2
Injection site warmth	11	0.2

17.2 This study poses a minor increase over minimal risk as it does not hold the prospect of direct benefit for the individual subject, but the

intervention presents an experience that is reasonably commensurate with those inherent to the subject's medical situation and is likely to yield generalizable knowledge about the disorder which is of vital importance to the detection of VOD/SOS. Physicians will be blinded to the results of the imaging.

18.0 Potential Benefits to Subjects

18.1 There are no potential benefits to subjects for participation to this study.

19.0 Investigator Assessment of Risk/Benefits Ratio: (IRB makes the final determination) *Based upon your response in Sections 17.0 and 18.0, please provide your assessment of risk and benefits in below table.*

Select as applicable:	**Pediatric Risk Category:**	
	Category 1	Research not involving greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51)
	Category 2	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR §46.405 and 21 CFR §50.52)
X	Category 3	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR §46.406 and 21 CFR §50.53)
	Category 4	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR §46.407 and 21 CFR §50.54)
Select if applicable:	**Adult Risk Category:**	
	Not Greater than Minimal Risk	
	Greater than Minimal Risk	

20.0 Data Management and Confidentiality

20.1 All identifiable data will be stored in REDCap and InteleViewer (PACS viewing system used by Department of Radiology) housed at CMH and will be password protected. Patient DOB, MRN and exam date and type are necessary to identify data points of interest. A separate master linking list with patient MRN will be kept within CMH internal server and will be destroyed upon completion of the study. All recorded dates (e.g. dates of US SWE, HCT and conditioning regimen) will be destroyed upon completion of data analysis.

20.2 Dr. Averkiou will have access to our Research PACS, which is a limited to exams performed for research purposes. These exams are manually placed into the research PACS by a member of the radiology research team. All data in the research PACS is

identifiable for purposes of this research study, but Dr. Averkiou will only access this information as part of this research study.

20.3 A certificate of confidentiality will not be sought for this study.

20.4 Study data will be evaluated by the PI throughout the duration of the study for QA.

20.5 Patient information will be maintained in a REDCap application and will be housed within the CMH Data Center by the Division of Biomedical Informatics. The hosting server has an internal failover two-node cluster. The CMH Data Center is constantly staffed by qualified personnel and physical access is limited to authorized personnel. The Center has optimized conditions for the servers and stabilized electrical supply. The database has a full backup. The database server is located inside the CMH corporate firewall. A person must have CMH system access to loin. Additional security for the study patient database restricts access to only those persons specifically granted authorization by the Principle Investigator. It is possible for data to be downloaded from REDCap. Individuals who lack authority to see confidential data can download reports with non-identifiable data only. The core research group will have the ability to download sensitive fields and if such a download occurs, REDCap maintains a record of who, what, when, and to where copies of the database were imported.

20.6 Consented subjects will be provided a printed calendar outlining their research ultrasound schedule at the time of admission for the duration of their enrollment in the study. Each calendar will be specific to each subject's treatment and clinical course, which is being performed as standard of care.

For subjects that are enrolled in additional research ultrasound studies, all research ultrasound exams will be listed on the same calendar.

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

21.1 Describe:

- All data collected on subjects who receive study drug will be analyzed for safety. The proportion of patients with specific adverse events will be reported as well as the worst grade observed across all adverse events. The maximum confidence interval width for these estimates is 16.8%. If the observed estimated adverse event proportion is 10%, the 95% confidence interval is (5.3, 15.6%).
- Safety information will be collected at the time of study visit when the patient is monitored during contrast administration.
- Safety data collection will begin with the first participant and participants will be monitored in real time.

- The PI or an assigned co-investigator will be responsible for monitoring the data.
- Cumulative data will be reviewed on a weekly basis beginning with the first study participant.
- All data collected on subjects who receive study drug will be analyzed for safety. The proportion of patients with specific adverse events will be reported as well as the worst grade observed across all adverse events. The maximum confidence interval width for these estimates is 16.8%. If the observed estimated adverse event proportion is 10%, the 95% confidence interval is (5.3, 15.6%).
- Any adverse event resulting from the contrast agent requiring an ICU admission will trigger an immediate suspension of the research.

22.0 Provisions to Protect the Privacy Interests of Subjects

22.1 Privacy interests for subjects will be maintained by limiting interaction with subjects and LAR to only study personnel at the discretion of the treating physician.

22.2 This study is voluntary, the physicians involved do not have any financial gain or interest with the study. Subjects may withdraw participation at any time and their care and treatment at CMH will not be compromised. Subjects and their families will be told that there participation is voluntary and that they may stop at any time.

22.3 Only IRB approved members of the study team will be granted access to the study folder located on the network drive or the REDCap database. Additionally, study team members who are responsible for collected data only will be granted limited access to REDCap, allowing them to record data only.

22.4 PHI to be accessed and/or recorded for this research study includes: DOB, MRN, dates of service (US SWE exams, conditioning regimen, HSCT, lab dates and dates of severity milestones and death of applicable) will be recorded.

22.5 HIPAA authorization will be wrapped into permission/assent/consent form.

23.0 Compensation for Research-Related Injury

23.1 Regular clinical review will minimize the risk of complications or harm as a result of study participation. In the event that an adverse event results from the study procedure, it will be reviewed by the principal investigator, reported to the IRB, and dealt with per institutional policy. Treatment will be available at CMH and will be provided at the usual charge. Payment for this treatment will be the participant's responsibility as this research study does not have funds

set aside to pay research participants if the research results in harm or complications. The approved IRB P/A/C will include known possible adverse events of study participation as well as payment responsibility for any adverse event.

24.0 Economic Burden to Subjects

24.1 There is no costs to patients for participating in this research study. Patients who agree to study participation will not be charged for the ultrasound examinations or Lumason contrast agent.

25.0 Permission/Assent/Consent Process

25.1 Indicate whether you will you be obtaining permission/assent/consent, and if so describe:

- P/A/C will take place in clinic, radiology department of inpatient floor prior to start of conditioning regimen.
- Subjects will be given time to review the P/A/C for consent up to the day before the start of conditioning regimen to ensure that pre-BMTT US abdominal limited, Doppler, CEUS and SWE can be performed.

Subjects who are not yet adults (infants, children, teenagers)

One parental/LAR permission will be required for all subjects under the age of 18.

Subjects over the age of 7 will be required to provide assent for the study and will be documented on P/A/C.

Consent at 18 years of age, when minor subjects become adults

25.2 Subjects that turn 18 years of age during the study period will be re-consented with a short form addendum for continuation in the study.

Non-English Speaking Subjects

- P/A/C forms will be translated into Spanish and Arabic by ORI Translations program.

26.0 Process to Document Permission/Assent/Consent

26.1 P/A/C will be documented by CMH research policy.

27.0 Setting

27.1 Describe the sites or locations where your research team will conduct the research.

- Subjects will be identified by treating BMT physician and will be approached for consent in clinic, radiology department or inpatient floor.
- Research procedures will be performed at CMH Adele Hall according to site specific regulations and standards.

28.0 Resources Available

28.1 Describe the resources available to conduct the research: For example, as appropriate:

- From our preliminary data, patients with no SOS or mild SOS have an average increase in velocity over baseline of 0.056 m/s at day +5 with (SD of 0.22 m/s). Our four patients with moderate and severe SOS who received defibrotide had an average increase in velocity over baseline of 0.25 m/s at day +5 (SD 0.185 m/s), we would need 245 patients (13 with moderate or severe SOS and 232 with no SOS or mild SOS) to have a power of 80% to detect a difference with alpha of 0.05. We perform approximately 40 HSCT transplants at CMH every year and in combination with the other sites, we anticipate an enrollment rate of >60% to appropriately recruit enough subjects to complete the study.
- We anticipate needing two years to recruit enough subjects to appropriately power the study and an additional one year to analyze results.
- CMH radiology department has three GE Logiq E10 ultrasound machines and 12 dedicated sonographers to perform the imaging requirements.
- IDS pharmacy will supply the Lumason Contrast agent.
- All participating sites will be required to obtain IRB approval at their local institution and CMH research coordinators will ensure all modifications, amendments, continuing reviews and AE/SAE's are electronically transferred to each site. Study SOP will be utilized for document transfers and documentation of receipt will be kept.

29.0 Multi-Site Research

29.1 Study-Wide Number of Subjects: 80

29.2 Study-Wide Recruitment Methods: CMH will be the only site recruiting subjects. The University of Washington – Seattle's involvement is to provide imaging consulting. Dr. Averkiou will have access to our PACS system for evaluation of the imaging for analysis and image protocol validation.

- All required approvals (initial, continuing review and modifications) will be submitted to CMH IRB (IRB of record) for approval and letter of correspondence provided by CMH IRB will be sent to each site for local IRB (relying IRB) approval. Each site will be required to send documentation of local IRB approval.
- All modifications will be communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements and any unanticipated problems will be reported in accordance with local policy.

29.3 Describe the method for communicating to engaged participating sites:

- All education and training to researchers and research staff will be provided by CMH and documentation of training will be recorded.
- All reportable events must be communicated within 5 business days of notification of reportable event to CMH study staff for submission to CMH IRB (IRB of record).
- Interim results will be communicated through virtual meetings and electronic communication as they become available.
- The closure of a study will be communicated through electronic documentation of correspondence letter from IRB of record to participating sites for relying IRB documentation.
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30.0 International Research

29.1. NA